



Overview of antigen-sparing and delivery technologies



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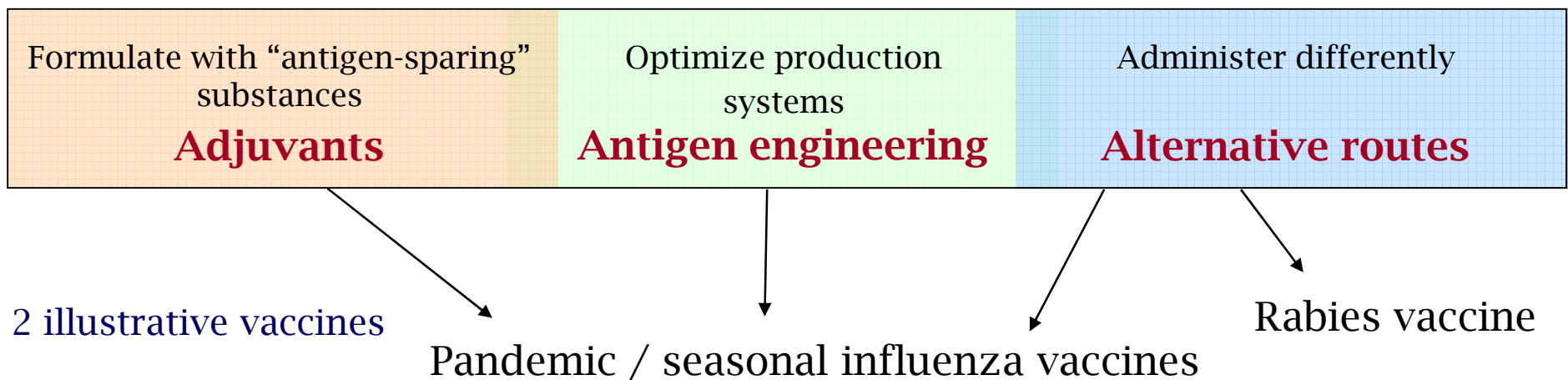
Antigen-sparing: a technology to increase vaccine availability

- Antigen is usually the most expensive part of a vaccine (e.g. rabies vaccine)
- Public health needs can exceed global antigen production capacity (e.g. pandemic influenza immunization)

How to increase vaccine availability / affordability?

➡ "Antigen-sparing" appears as a promising avenue

Reducing antigen content to increase the number of vaccine doses per production unit



Outline

Adjuvants for antigen-sparing

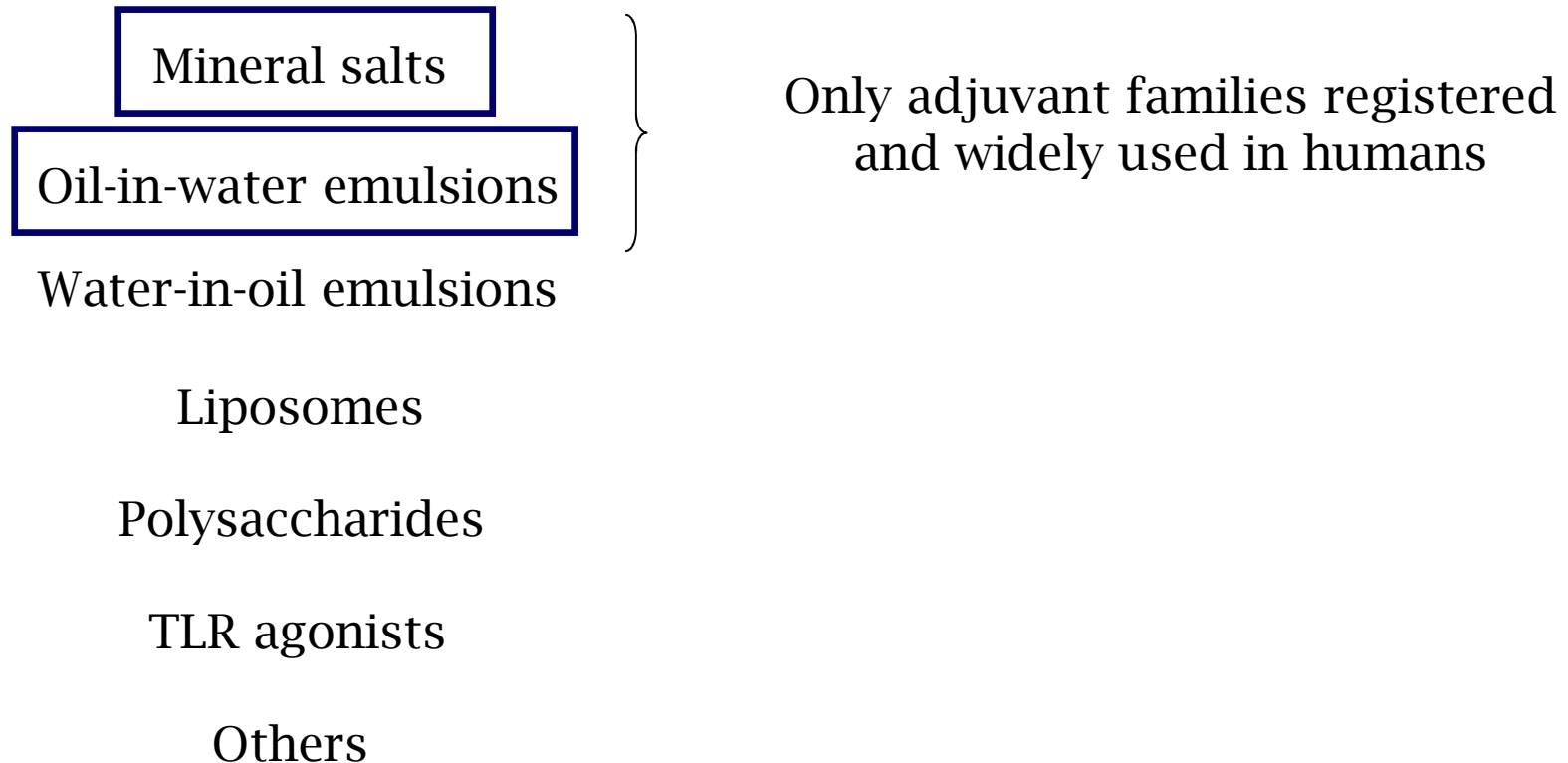
Antigen engineering for optimization of production systems

Alternative vaccine delivery routes for dose-reduction

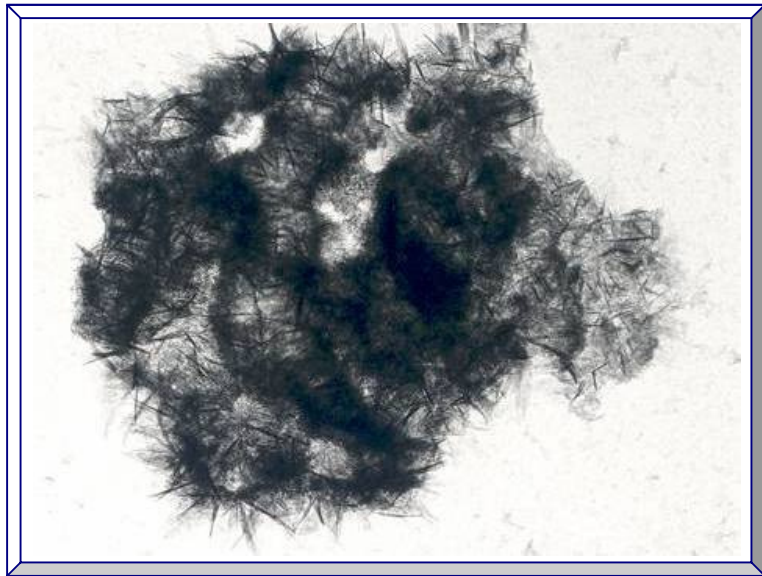
Adjuvants for antigen-sparing

Adjuvant: a substance that enhance, re-direct, and / or sustain the immune response to a co-administered antigen

➡ Potential for antigen-sparing effect



Aluminum salts



Aluminum oxyhydroxide

Used in many licensed vaccines:
D, T, P, HepA, HepB, HiB...

Trigger mainly a *Th2* immune response

Mode of action yet to be fully elucidated

Enhance antigen stability

Extensive safety record

➡ Billions of people including infants have received aluminum adjuvanted-vaccines

For several vaccines, aluminum salts can decrease the amount of antigen and the number of doses needed: **antigen-sparing**

Aluminum salts in influenza vaccines

Seasonal influenza vaccines

Low to moderate immunopotentiality

Potential safety concerns with repeated yearly administration of aluminum salts

➡ Used in only one seasonal influenza vaccine

Fluval AB (Omninvest, Hungary): whole inactivated virion adjuvanted with AlPO₄

Pandemic influenza vaccines

H5 inactivated virion: 90 µg HA (2 doses) needed for meeting registration criteria

Aluminum salts tested in clinical trials for several whole virion-, split virion- and subunit candidate pandemic vaccines

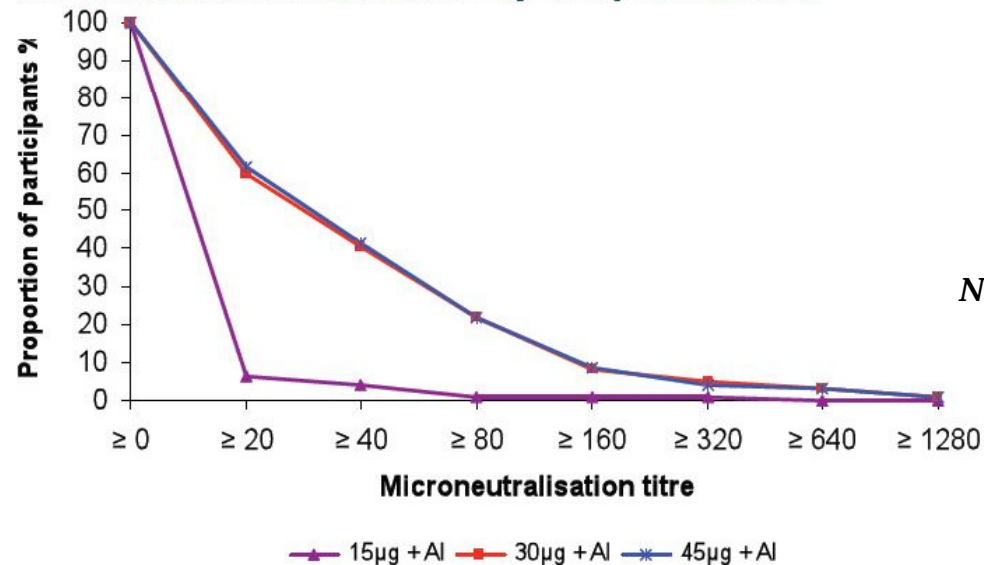
Aluminum salts in pandemic influenza vaccines

Pandemic influenza vaccines

H5 inactivated virion: 90 µg HA (2 doses) needed for meeting registration criteria

.Split H5N1 virion + AlOH \longrightarrow 30 - 45 µg

Microneutralisation antibody 6m post dose 2



Nolan et al., 2008

➡ Moderate antigen-sparing effect for pandemic influenza vaccines

Pros and cons of aluminum salts

Pros

No intellectual property barriers,
relatively little technological hurdles

Cheap to produce

Extensive safety record

Enhancement of antigen stability

Cons

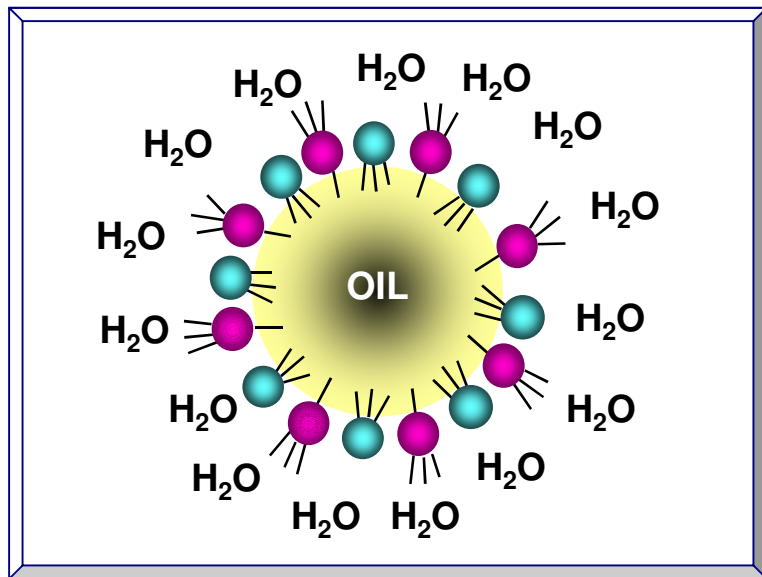
Utility highly dependant on antigen

Accidental freezing will damage the
vaccine

Potential safety concerns with
repeated administration

Moderate antigen-sparing effect observed
for influenza vaccines

Oil-in-water emulsions



Different from water-in-oil emulsions

Appearance: milky

Composition:

Squalene: shark oil

Surfactants

Water

+ / - DL- α tocopherol

+ / - block copolymer

+ / - immunostimulants

MF59 (Novartis), AS03 (GSK),
AF03 (Sanofi-Pasteur), SE (IDRI)...

Oil-in-water emulsions vary in their composition

Can be added extemporaneously: production / logistic advantage

Oil-in-water emulsions in seasonal influenza vaccines

Seasonal influenza vaccines

Limited adjuvant effect of oil-in-water emulsions in adults

Frey et al., 2003

Significant adjuvanticity in young subjects (limited cross-reactivity)

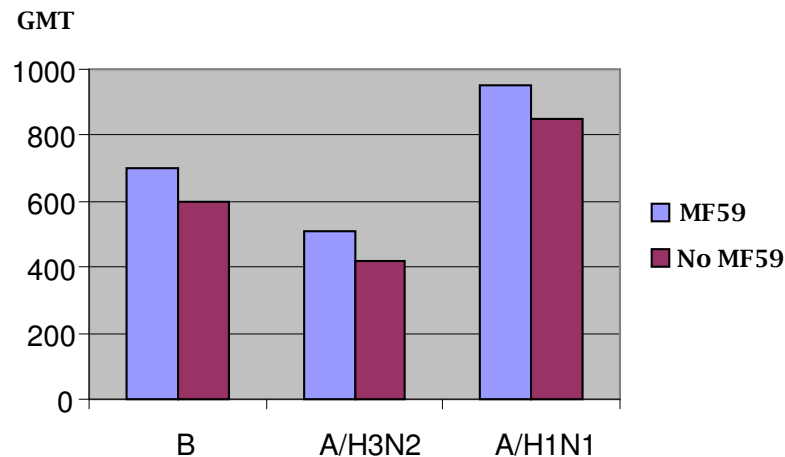
Vesikari et al., 2009

Hancock et al., 2009

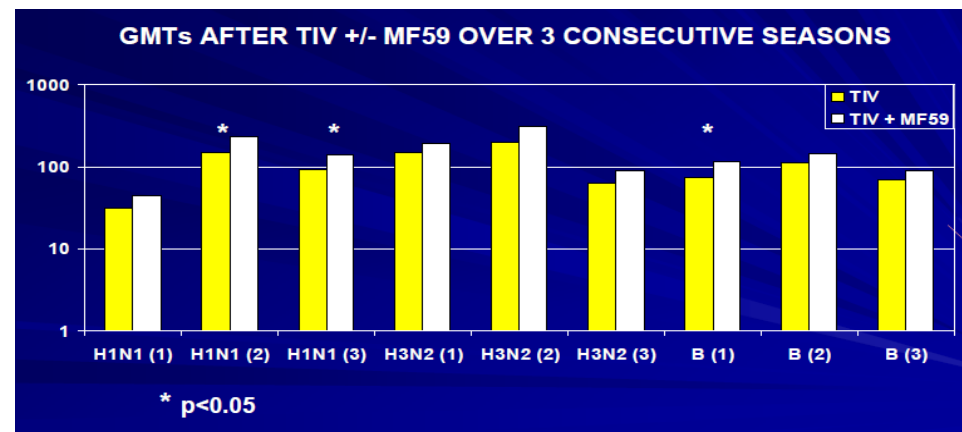
➔ Used in only one seasonal vaccine for elderly

Minutello et al., 1999

Fluad (Novartis): subunit virion adjuvanted with MF59™



Frey et al., 2003



Adapted from Minutello et al., 1999

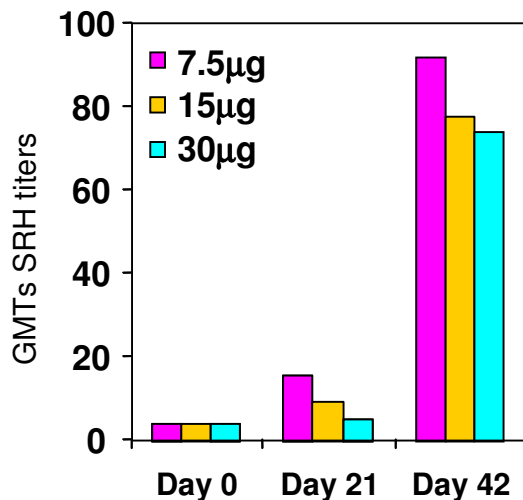
Oil-in-water emulsions in pandemic influenza vaccines

Pandemic influenza vaccines

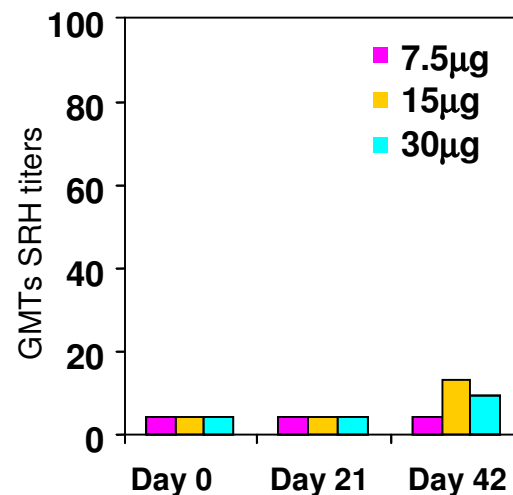
H5 inactivated virion: 90 µg HA (2 doses) needed for meeting registration criteria

- . Subunit H5 virion + MF59 → 7.5 µg
- . Split H5 virion + AS03 → 3.8 µg
- . Split H5 virion + AF03 → 3.8 µg

MF59TM-adjuvanted H5N3 vaccine



Non-adjuvanted H5N3 vaccine



Nicholson et al. 2001

Pros and cons of oil-in-water emulsions

Pros

Cheap, feasible, stable

Extensive safety record
(>140 M people including infants)

Possibility for
extemporaneous combination

Cons

Higher incidence of mild adverse
reactions

Public perception of the safety of
adjuvants (especially for squalene)

Role of pre-existing immunity not fully
understood

Remarkable antigen-sparing for pandemic influenza vaccines



**Quick conversion of unadjuvanted seasonal vaccine capacity into
adjuvanted pandemic vaccine capacity:**
(expected multiplication factor: 5 to 25)

Outline

Adjuvants for antigen-sparing

Antigen engineering for optimization of production systems

Alternative vaccine delivery routes for dose-reduction

Antigen engineering

The power of new technologies...

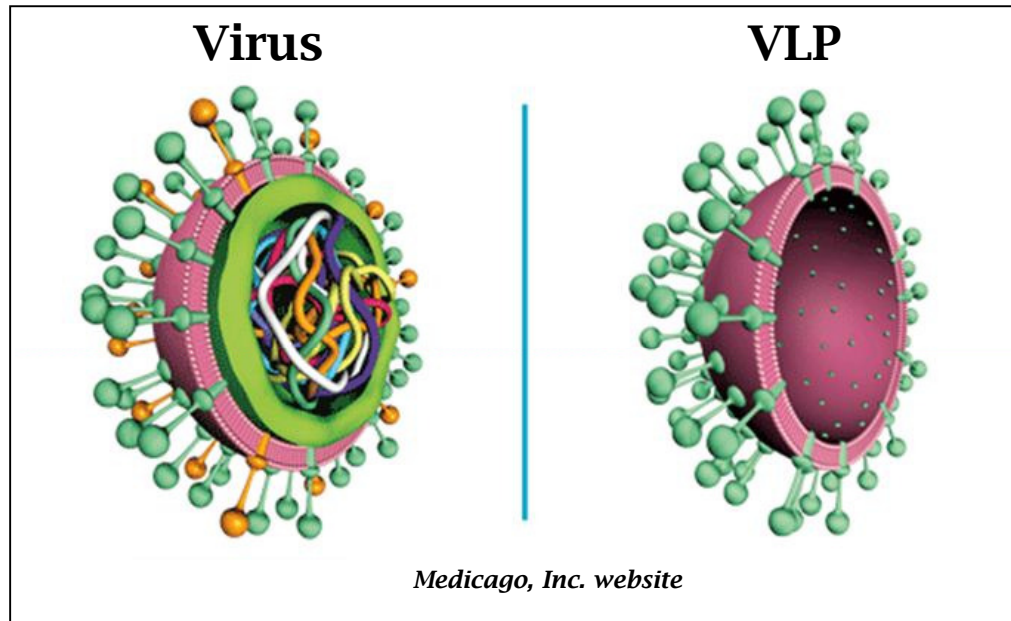
- . Molecular engineering of antigen structure for better immunological presentation

- . Production yields optimization

- ➡ How can we make more efficacious vaccine doses per unit of production?

Goal: reduction in cost of production, increase in vaccine production capacity

Optimized antigen presentation: virus-like particles



Multimeric presentation
T-independent maturation of B
cells, enhanced density of T-cell
epitopes...

VLP products:
HepB and HPV vaccines: licensed
Malaria RTS,S in phase III

- . Only licensed technology for recombinant human subunit vaccines
- . Increases intensity of immune responses

Antigen-sparing potential

Recombinant expression systems

1. Protein expression systems *(presentation by Thomas Warf)*

Baculovirus-infected insect cells *(presentations by Manon Cox and Rahul Singhvi)*,
yeast, plants *(presentation by Vidadi Yusibov)*, fungi

2. Viral vectored-vaccines

Adenoviruses, MVA, alphaviruses, retroviruses...

3. Peptides

4. DNA vaccines

Plasmid-based (ex: M2, M2+NP, M2+NP+HA)

Potential for more effective and accelerated production process

Possible targeting of conserved / alternative targets epitopes

Safety, correlates of protection, and regulatory scrutiny to consider

Amenable to large production capacity increase, as compared to
mammalian cell culture or eggs

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Vaccine delivery routes

Alternative routes to intramuscular vaccine delivery:

Intranasal, sublingual, oral, intrapulmonary, subcutaneous, intradermal...

Expected roles of vaccine delivery optimization:

- . Increased immunogenicity in special groups
- . Reduced infectious waste and exposure to infectious material
- . Better acceptability
- . Reduced need for skilled health force

➡ [Antigen-sparing](#)

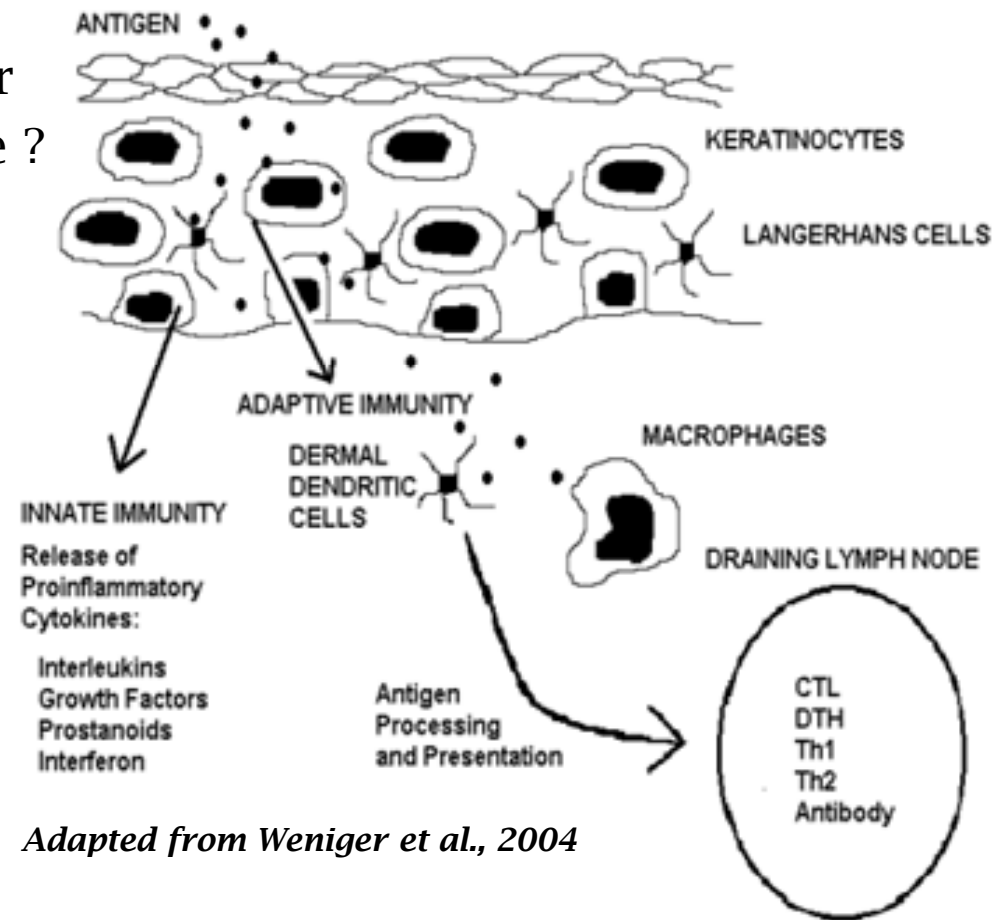
Intradermal route has been investigated extensively for dose-sparing potential



Dose-sparing by intradermal delivery of vaccines?

Is the dermis really a better site for immune induction than the muscle ?

What is the evidence that dose-reduction follows ID delivery?

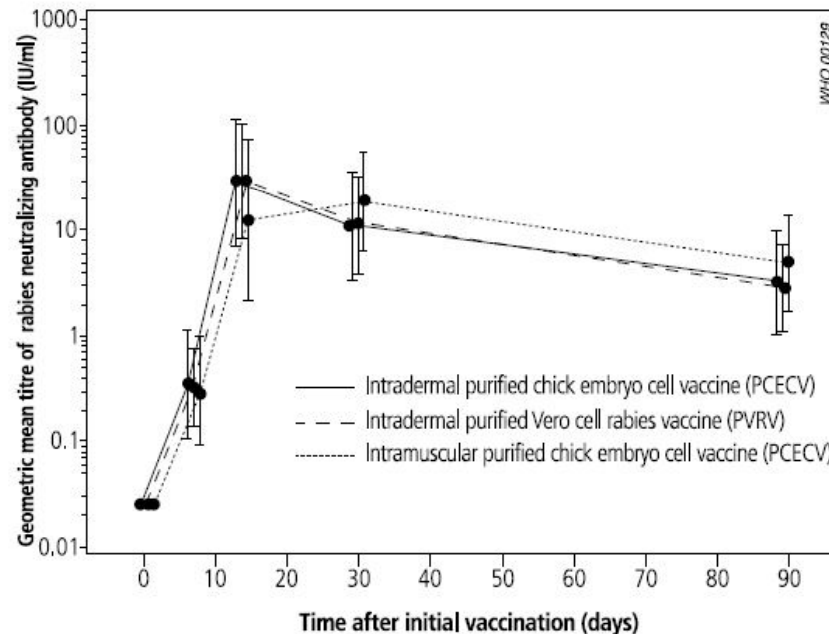


Adapted from Weniger et al., 2004

ID delivery of rabies vaccines

Demonstration of dose-reduction by ID route has led to a policy recommendation on ID schedules ("Thai Red Cross schedule") by WHO in 2007

Fig. 1. Concentration of rabies neutralizing antibody (per protocol population)



→ ID vaccine doses: 0.1mL
→ IM vaccine dose: 1.0mL

Briggs et al., 2000

Antigen-sparing can be achieved by ID administration for some vaccines

By **Maggie Fox**, Health and Science Editor
WASHINGTON | Mon Sep 13, 2010 4:56pm EDT

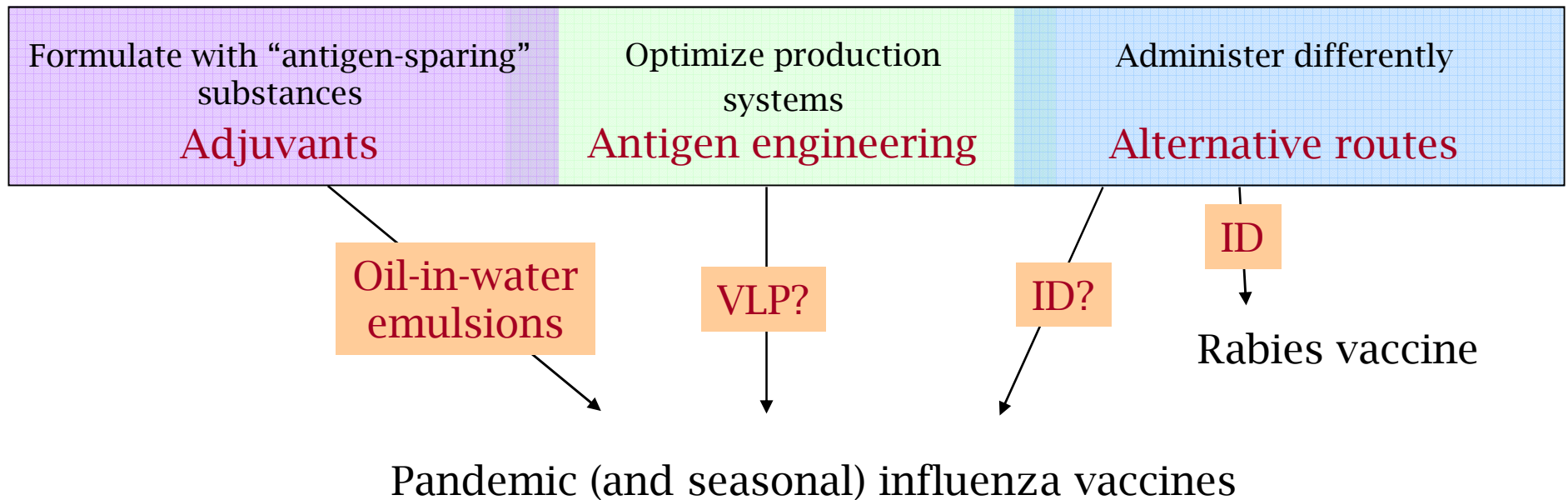
(Reuters) - Vaccine maker Sanofi Aventis asked U.S. regulators on Monday to approve a new flu vaccine that uses a short, thin needle.

Sanofi says the new vaccine, developed with syringe maker Becton Dickinson, may hurt less than standard vaccines, does a better job of stimulating protection against influenza, and requires less of the active ingredient.

The company said the U.S. Food and Drug Administration had accepted the application and it hoped the agency would decide whether to approve it by early next year. The vaccine is approved for use in Europe.

"We believe that Fluzone Intradermal Vaccine could be an important tool in increasing adult immunization rates due to its ease of use for health-care providers and the high level of interest expressed by patients for this immunization option," Wayne Pisano, president and chief executive officer of the company's Sanofi Pasteur vaccine unit, said in a statement.

Antigen-sparing and delivery technologies





Global Adjuvant Development Initiative

Missions of the WHO **Global Adjuvant Development Initiative:**

1. Supply portfolio of proven adjuvants **accessible to public sector**
2. Provide vaccine formulation **services** and **training courses**
3. Facilitate **technology transfer** of adjuvants towards developing countries



2010: creation of a center of excellence
in **Vaccine Formulation and Adjuvants**
at University of Lausanne, Switzerland

UNIL Vaccine Formulation Laboratory

Establishment as a **adjuvant technology transfer hub**

2011: Technology transfer of an oil-in-water emulsion towards DCVM for pandemic influenza

Hands-on training courses in vaccine formulation

The hub will facilitate **adjuvant access** for public sector / developing countries

Programme supported by:

- European Commission
- Wellcome Trust
- HHS/BARDA



PUBLIC - PRIVATE PARTNERSHIPS

VACCINE DEVELOPMENT SELF-SUFFICIENCY



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Developing Countries Vaccine Manufacturers' Network



Bharat Biotech



University of Lausanne

